IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Maes, et al.

Serial No.: 09/773,351 Group Art Unit: 1617

Filed: January 31, 2001 Examiner: Cotton, Abigail Manda

For: Cholesterol Sulfate and Amino Sugar Compositions for Enhancement of Stratum Corneum Function

REMARKS

The Examiner rejects Claims 1 and 3 to 20 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-21 of copending Application No. 10/424,616. The claims of the copending Application are believed to be still pending. Applicants again acknowledge the provisional double patent rejection made by the Examiner. However, in light of the arguments set forth below, Applicants will make a terminal disclaimer, if necessary, in the event that allowable subject matter is indicated. With respect to the substantive nature of the Examiner's rejections, Applicants assert that neither one of the Ribier references teaches a mixture that has components that form a unit with one another.

> [T]he Examiner respectfully notes that the claims recite an "integral mixture," which given its broadest possible reasonable interpretation means a mixture that has components that form a unit (i.e., a composition) with one another, which is taught by the Ribier et al. references, and includes even compositions having distinct phases and vesicles, as these phases and vesicles nonetheless make up parts of a single unit (the composition).

This is, according to the Examiner in the final office action, consistent with the definition of "integral" found in the Merriam-Webster Online Dictionary. However, the Examiner in the final office action finds that this is what is taught by the Ribier et al. references (U.S. Patent Nos. 5,650,166 and 5,925,364) because the distinct phases and vesicles make up part of a single unit (the composition). To recap, Claims 1 and 3 to 9 of the present invention were rejected under 35 U.S.C. §102(b) as being anticipated by Ribier et al. (5,650,166) and Claims 13 to 20 were rejected under 35 U.S.C. 103(a) over Ribier et al. (5,650,166) for the following reasons.

> Ribier et al. discloses a moisturizing composition for the treatment of surface and deep layers of the skin clear comprising the instant ingredients such as cholesterol sulfate in the salt of alkali metal (including potassium)(see col. 3, lines 64-67), N-acetylglucosamine (see col. 5, lines 59-67), the particular sterol, cholesterol (see col. 3 line 60 and col. 6, lines 47-49), fatty acids, including linoleic acid (see col. 6, lines 44-46.) Ribier et al.

> further teaches the use of plant extracts (see col. 7, lines 5-8.) The compositions of Ribier et al. may be an emulsion, gel, lotion, and ointment form (see col. 7, lines 10-14.)
>
> Thus the disclosure of Ribier et al. anticipates claims 1 and 3-9. . . .
>
> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the amount of the known particular agents taught in Ribier et al.

Further, Claims 1, 3-4, 6-9, 11 and 18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ribier et al. (5,925,364) in view of Sebag et al. (5,411,742) for the following reasons.

> One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular fatty acid, linoleic acid, and cholesterol in the composition of Ribier et al, since fatty acids broadly and the particular fatty acid, linoleic acid, and known to be useful in a cosmetic or dermatological composition for treating skin based on the prior art. Moreover, cholesterol is well known to be used as a cosmetic or dermatological composition for treating skin according to Sebag. Therefore, one of ordinary skill in the art would have reasonably expected that combining the composition of Ribier et al and the composition of Sebag known to be useful for the same purpose, treating skin, in a composition to be administered would improve the therapeutic effect for treating skin, in a composition to be administered would improve the therapeutic effect for treating skin.

Further still, Claims 10-12 and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ribier et al. (5,650,166) in view of Subbiah (6,150,381) and Ichinose et al. (5,702,691) for the following reasons.

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Ribier et al. by the addition of sclareolide for its anti-acne properties as taught by Subbiah and by the addition of white birch extract for its anti-inflammatory properties as taught by Ichinose. The motivation for modification comes from the benefit of such properties in formulating cosmetic compositions. The missing ingredients have art-recognized suitability for the intended purpose of formulation cosmetic compositions.

Applicants respectfully traverse the line of reasoning presented by the Examiner in the final office action because the Ribier et al. references fail to teach or suggest a unit (the composition). The reference point with respect to the "unit" is not the composition because any composition could be considered a unit. The issue is what is occurring throughout and within the unit. The comparison that probes the issue is at the level of cholesterol sulfate and the exfoliant. In the present invention, these two components are an integral mixture in the composition, and this is in stark contrast to the Ribier et al. references where cholesterol sulfate and N-acetylglucosamine are separate and distinct and in no way are integrated throughout and within the unit (the vesicle or the composition). While it is true that the

cholesterol sulfate and another component are confined within a unitary space, i.e., the vesicle or composition, this does not lead to the conclusion that the cholesterol sulfate is a unit with the components in the other layers of the vesicle. This is what separates the Ribier et al. references from the present invention and one of ordinary skill in the art would readily know and understand this difference.

The cholesterol sulfate in one layer of the Ribier vesicle is not mixed with the N-acetylglucosmine of any of the other layers of the vesicle. Rather, the cholesterol sulfate layer is separated from the N-acetylglucosmine layer of the vesicle. No mixing of cholesterol sulfate in one layer of the Ribier vesicle occurs with the N-acetylglucosmine layer of the Ribier vesicle. However, unlike the Ribier references, the present invention is an integral mixture of cholesterol sulfate and an exfoliant throughout and within the composition that produces the integrated result of a balanced nurturing of the skin barrier. Therefore, the integral mixture of the present invention is not disclosed, taught or suggested by the Ribier references. As the Ribier references are the primary reference in the remaining §103 rejections, none of the remaining rejections result in a disclosure, teaching or suggestion of the present invention. At best, the Ribier reference could be interpreted as teaching how to bring cholesterol sulfate and N-acetylglucosamine in close proximity to one another but not as a mixture and certainly not as an integral mixture. None of the secondary references remedy the defect of the Ribier references.

The Examiner notes that the only reference to "integrated" is with respect to the "integrated results" mentioned on page 4, lines 22 to 24, of the present specification. Therefore, the Examiner finds that there is no support in the specification under 35 U.S.C. §112, first paragraph for an "integral mixture" that excludes compositions having vesicles of two or more phases. Applicants respectfully traverse this rejection because the integrated result is only rendered by the integral mixture. The result is inextricably bound to the mixture because it is only by virtue of the mixture that the result is achieved, and therefore, the mixture is like the result integral. The integrated result further supports Applicants' argument above regarding the §102 and §103 rejections with respect to the Ribier references. With the Ribier references, producing an integrated result is not an issue because the cholesterol sulfate and N-acetylglucosamine remain in separate layers of a vesicle presumably in order for them to exhibit their individual activities without concern for canceling each other out with respect to their activity. However, the surprising result achieved with the present invention is the fact that the cholesterol sulfate and exfoliant do not need to be separated. They can be combined in an integral mixture of the present invention and provide a benefit to the skin. One of ordinary skill in the art as noted in the present specification at page 4, lines 5 to 24, would have expected the two components having opposing activities to cancel each other out in a mixture and not produce an integrated result. But, to the contrary, it has been unexpectedly found with the present invention that the two opposing components do not

cancel each other out. This would never have been found based on the separated components of the Ribier references.

While Applicants refrain from speculating on a specific method for forming separate lipid layers, Applicants note that it is indicated in the Sebag reference at column 1, lines 38 to 54, that ionic amphiphilic lipids possess the property of forming mesomorphic phases and are capable of swelling in an aqueous solution to form a lamellar phase. After stirring in the presence of an aqueous solution, the Sebag amphiphilic lipids form vesicles dispersed in the aqueous solution. The Subbiah reference teaches a method for treating microbial infections with a sclareolide-like compound, and therefore, fails to provide any teaching of a cholesterol sulfate and an exfoliant in an integral mixture. Finally, the Ichinose reference teaches a flavanolol derivative for treating hair, and like the other secondary references fails to teach or suggest a cholesterol sulfate and an exfoliant in an integral mixture.

The arrangement in either of the Ribier references is not a unit nor is it an "integral mixture" in a vehicle as one of ordinary skill in the art would understand its plain meaning. Two ingredients that are separated from one another, as they are in the Ribier references by virtue of the vesicle formation, are not integral with one another. There is no integration where there is separation. Even if the interpretation of one of ordinary skill in the art were that a lipid vesicle containing cholesterol sulfate in the membrane layer and NADG encapsulated therein was equivalent to the integral mixture of the present invention, Applicants assert that it would be rebutted by the surprising results of the present invention. The Examiner asserts in the final office action that the Example in the present specification provides no clear and convincing evidence of nonobviousness or unexpected results since it is not a direct comparison between the present invention and the cited prior art references. However, Applicants previously note that all evidence of nonobviousness must be considered. *In re Soni*, 44 USPQ2d 1684, 1687 (Fed. Cir. 1995). Unexpected results must be sufficient to overcome a clear and convincing showing of obviousness. *Richardson-Vicks Inc. v. The Upjohn Co.*, 44 USPQ2d 1181, 1188 (CAFC 1997). As previously noted, a clear and convincing showing of obviousness has not been made. However, even if such a showing were made, comparative test results are not the only evidence that can be presented to overcome a clear and convincing showing of obviousness. The unexpected result in the present invention lies in the fact that two opposite acting agents are combined and do not cancel out their activity.

As Applicants have pointed out above and in previous responses, the systems in the cited prior art and that of the present invention are not the same, and there is no reason to believe that the integral mixture of the ingredients directly in a vehicle would necessitate a comparison with a lipid vesicle as these are two completely different systems and different arrangements of the components. To support this fact, Applicants previously submitted a copy of an article, Bouwstra et al., "Cholesterol sulfate and

calcium affect stratum corneum lipid organization over a wide temperature range" Journal of Lipid Research, vol. 40, 2303-3212 (Dec. 1999). In the article, the authors note that reduced levels of cholesterol sulfate contribute to desquamation, thus indicating that the presence of cholesterol sulfate would maintain the integrity of the stratum corneum and prevent desquamation. Therefore, Applicants maintain that one of ordinary skill in the art would expect a combination of cholesterol sulfate and an exfoliant to have no effect on the surface on the skin because while the exfoliant would contribute to desquamation, the cholesterol sulfate would act to prevent desquamation.

CONCLUSION

The present invention, as amended, is an integral mixture of an exfoliant and a cholesterol sulfate in a cosmetic or pharmaceutical vehicle that is not taught or suggested by the cited references describing lipid vesicles having one bilayer containing N-acetyl D-glucosamine, and another bilayer containing cholesterol sulfate as the components are arranged differently. Because none of the cited references alone nor in combination would lead one of ordinary skill in the art to the compositions and methods of the present invention, a *prima facie* case of obviousness has not been established. Applicants request therefore, that the Examiner's rejections under 35 U.S.C. §§102 and 103 be withdrawn. In view of the arguments presented above in the present submission, the claims are believed to be in condition for allowance, and issuance of a Notice of Allowance is respectfully solicited.

Respectfully submitted,

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